In Vivo Magnetic Resonance Elastography in Pediatric Brain Tumor Models

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Target Audience. This work would be of interest to preclinical and clinical researchers in the field of neurological and pediatric cancer, and those interested in the applications of MR elastography.

Introduction. There is an unmet need for refined imaging strategies that could improve the non-invasive diagnosis and management of children with brain malignancies. Magnetic resonance elastography (MRE) exploits the ability of MRI to visualize the propagation of shear waves resulting from vibrations applied to the cranium to quantify the viscoelastic properties of brain and tumor tissue, both preclinically and in patients (1,2). The altered viscoelastic properties of tumors compared with the surrounding brain parenchyma, combined with the sensitivity of MRE for differences in tumor microstructure (2), establishes MRE as an attractive modality for the detection and differential diagnosis of brain malignancies. Pediatric brain malignancies possess distinctive underlying biologies that discriminate them from adult tumors, even within a common neuropathological diagnosis such as glioblastoma (GBM) (3). The aim of this study was to determine whether the potential of MRE in the neuroradiological management of patients with brain malignancies could also be applied to the pediatric population. To test this, we investigated the viscoelastic properties of two pediatric brain tumor models, i) orthotopically implanted D-212 MG GBM xenografts and ii) GTML/*Trp53*$^{KI/KI}$ transgenic mice that spontaneously develop aggressive medulloblastomas, which faithfully emulate high-risk childhood GBM and medulloblastoma, respectively (4,5).

Methods. NCr *nu/nu* mice bearing orthotopic tumors derived from D-212 MG pediatric giant cell GBM cells (n=7, mean volume 19±3mm^3, mean 45 days after implantation), GTML/*Trp53*$^{KI/KI}$ transgenic mice bearing MYCN driven, p53 depleted medulloblastomas (n=3, mean volume 32±0.4mm^3, mean 42 days old), and non-tumor-bearing control mice (n=6), underwent MRE, performed on a 7T Bruker MicroImaging system using a 3cm birdcage coil. Axial T_2-weighted RARE images (150µmx150µm in plane resolution) were first acquired to localize the tumor. Subsequently, 3D steady-state MRE data were acquired using a vibration frequency of 1000Hz. Quantitative maps of G_d (elasticity) and G_l (viscosity) were reconstructed with an isotropic pixel size of 300µm (2).

Results. Parametric maps and histogram analysis of the distribution of G_d showed pronounced contrast and reduced elasticity between both D-212 MG and GTML/*Trp53*$^{KI/KI}$ tumors and the surrounding brain (Fig. 1A). Tumor ROIs drawn on T_2-weighted images correspond to the locations of the tumors as identified on H&E stained sections. Quantitative analysis of tumor ROIs revealed that both tumor types were significantly less elastic (D-212 MG G_d=3.85±0.15; GTML/*Trp53*$^{KI/KI}$ G_d=3.51±0.06) than the soft thalamic parenchyma in non-tumor-bearing mice (G_d=5.89±0.17; p=0.001 and p=0.02, respectively, Mann-Whitney), in addition to being less viscous (G_l) (Fig. 1B). Interestingly, all GTML/*Trp53*$^{KI/KI}$ tumors demonstrated a bimodal distribution of G_d, which reflects the more marked transition between the relatively stiffer rim and the softer core of GTML/*Trp53*$^{KI/KI}$ tumors compared with D-212 MG tumors observable on G_d maps.

Discussion. We demonstrate that two representative models of major high-risk pediatric brain malignancies share the unique softness characteristic of adult brain tumor models, allowing their detection by MRE (1,2). This supports observations that, clinically, pediatric GBMs are morphologically indistinguishable from adult GBMs (3). Although median G_d values were not sufficient to significantly discriminate between the two tumor types, the marked bimodal distribution of G_d in the GTML/*Trp53*$^{KI/KI}$ tumors was not apparent in D-212 MG GBM tumors. This biomechanical signature is, to date, unique to GTML/*Trp53*$^{KI/KI}$ amongst the brain tumor models we have investigated (1,4). Whilst ongoing histopathological investigation into growth patterns, vascular, cellular and extracellular networks will aid elucidation of the pathological determinants of this signature, these data reinforce the potential of MRE for discriminating tumor phenotypes on the basis of their mechanical properties.

Conclusion. This study demonstrates the potential of MRE for the detection and differential diagnosis of pediatric brain malignancies.

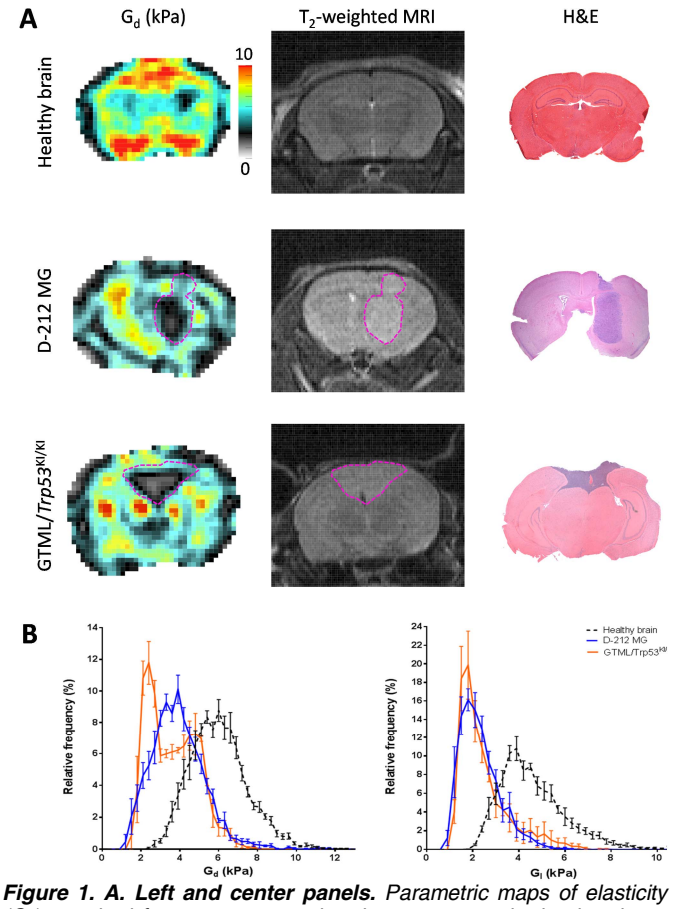

Figure 1. A. Left and center panels. *Parametric maps of elasticity (G_d) acquired from a non-tumor-bearing mouse, and mice bearing a D-212 MG pediatric glioblastoma xenograft or a GTML/Trp53*$^{KI/KI}$ *medulloblastoma alongside T_2-w MRI of the same imaging slice. (---) indicates the tumor boundary.* ***Right panel****. H&E staining of the same brains showing brain anatomy and tumor locations.* ***B.*** *Frequency histograms showing the distribution of elasticity (G_d) and viscosity (G_l) for healthy brain parenchyma, D-212 MG and GTML/Trp53*$^{KI/KI}$ *tumors over the whole cohorts.*

References. (1) Jamin *et al.*, *Proc. ISMRM.* 2013:0448. **(2)** Simon *et al.*, *New J Phys. 2013; 15*:085024. **(3)** Jones *et al.*, *Nat Rev Clin Oncol.* 2012;9:400-13. **(4)** Boult *et al.*, *Neuro Oncol* 2014;16(Suppl 1):1-157. **(5)** Hill *et al.*, *Cancer Cell* 2014; In Press.

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